

Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claim 1 has been amended, claims 3 and 6 have been cancelled without prejudice, and new claims 14-21 have been added. Descriptive support for new claim 14 appears in the first full paragraph on page 30 and the third full paragraph on page 35; descriptive support for new claim 15 appears in the first full paragraph on page 34; and descriptive support for new claim 16 appears in the first full paragraph on page 30. New claim 17 finds descriptive support in original claim 3 (i.e., claim written in independent form), and new claims 18-21 find descriptive support in original claims 3 and 8-13. Claims 1, 2, 4, 5, and 7-21 are pending, with claims 4 and 5 being withdrawn.

The amendments to the specification are made to correct typographical errors. In particular, the paragraph on page 103 is corrected to render the specification internally consistent. The specification at page 58, lines 17-18, clearly recites that *holB* was not identified by Deckert et al., 1998. Therefore, correction of the paragraph on page 103 does not constitute new matter.

Applicants respectfully request reconsideration of the restriction requirement imposed in the present application. Because of the relatedness of the subunits and their use together in a clamp loader complex (see, e.g., claims 9 and 19), applicants submit that the search of the related subcombinations would not be burdensome.

The objection to the specification is overcome by the above amendments. Although applicants disagree with the assertion made by the U.S. Patent and Trademark Office (“PTO”), the present claim language is clearly supported by the first full paragraph on page 30, along with the disclosure of the nucleic acid sequence of SEQ ID NO: 177 (and SEQ ID NOS: 179 and 181) and the corresponding amino acid sequence of SEQ ID NO: 178 (and SEQ ID NOS: 180 and 182).

The objections to claims 1, 3, and 6 are overcome by the above amendments and should be withdrawn. The objection to claims 1-13 as encompassing non-elected subject matter is noted, but no amendments have been made in this regard given applicants’ request for reconsideration (above).

The rejection of claim 7 under 35 U.S.C. §112 (second paragraph) for indefiniteness is respectfully traversed. The PTO has taken the position that the term “purified” is unclear in view of the language “isolated” as used in claim 1. Applicants respectfully disagree.

The term “isolated” connotes that the claimed subunit is in an environment that is distinct from that of the native subunit, i.e., the subunit no longer exists in a cellular environment. In contrast to a subunit that can exist, for example, in a protein extract obtained from a cell, a purified subunit is one that is substantially separated from other proteins. Both isolated delta subunit and purified delta subunit are described in the procedure recited in Example 19 for the recombinant expression of *A. aeolicus* delta subunit. In particular, Example 19 describes cell lysate containing the recombinant delta subunit (i.e., isolated but not yet purified protein), as well as the purification of delta subunit from the cell lysate (first via Heparin Agarose column and then via FFQ Sepharose column). Thus, “purified” and “isolated” are distinct terms, and persons of skill in the art would understand the distinction between these two terms.

For these reasons, the rejection of claim 7 is improper and should be withdrawn.

The rejection of claims 1, 2, and 4-13 under 35 U.S.C. §112 (first paragraph) as lacking written descriptive support is respectfully traversed.

The burden of establishing that an application lacks adequate written descriptive support falls on the PTO. *See In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.”). Hence, the PTO must demonstrate *why* the disclosure is insufficient.

The Federal Circuit has clearly espoused that *per se* conclusions of written description violations cannot be founded upon the basis of genus size alone. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1326-27, 63 USPQ2d 1609, 1614-15 (Fed. Cir. 2002) (refusing to adopt position that three species as a matter of law cannot satisfy written description requirement for significantly larger genus). Thus, the PTO’s conclusion cannot be based on genus size alone. But that is precisely what the PTO has done at page 5 of the outstanding office action. Because the PTO’s position is unsupported by law and

unsupported by any facts other than genus size, applicants submit that the PTO's position cannot be sustained.

In contrast, applicants present Exhibits 1-3 (attached hereto) as evidence that the nucleic acid sequence of SEQ ID NO: 177 and the corresponding amino acid sequence of SEQ ID NO: 178 represent the claimed genus. Exhibit 1 is a presentation of a Genbank accession for a thermophilic *Bacillus*, or *Geobacillus*, *holA* nucleic acid that is homologous to the nucleotide sequence of SEQ ID NO: 177. This *holA* nucleic acid was identified by a protein-protein BLAST search of the Genbank database performed using the amino acid sequence of SEQ ID NO: 178 and the BLAST default settings. Based upon alignments performed using Align® for nucleic acids and ClustalW for amino acids (using the European Molecular Biology Laboratory server and its default settings), this homolog shares about 98 percent identity at the nucleic acid level (Exhibit 2) and about 99 percent identity at the amino acid level (Exhibit 3). Thus, species of delta subunits from thermophilic organisms that belong to the biological classification *Bacillus* or *Geobacillus* clearly share similar structure and, therefore, function.

Applicants submit that the language recited in claim 1 is precisely the type of claim language that was acknowledged in *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) as being acceptable under the written description requirement. In *Eli Lilly*, the Federal Circuit addressed the validity of several claims of U.S. Patent No. 4,652,525 to Rutter et al. ("Rutter"), specifically those claims that recited the limitations 'vertebrate,' 'mammalian,' or 'human' cDNA for insulin. Rutter disclosed the nucleotide and amino acid sequences of a rat cDNA encoding insulin, and described a general procedure for obtaining the human cDNA encoding insulin. *Id.* at 1567, 43 USPQ2d at 1405. The Federal Circuit found that the description of the rat cDNA did not provide adequate descriptive support for the narrow subgenus of 'human' cDNA (no species disclosed), the larger subgenus of 'mammalian' cDNA (only the one rat species disclosed), and the larger genus of 'vertebrate' cDNA (only the one rat species disclosed). *Id.* at 1567-68, 43 USPQ2d at 1405. The Federal Circuit did acknowledge, however, the district court's statement that the specification provided adequate written descriptive support for the subgenus of 'rat' cDNA encoding insulin. *Id.* at 1566.

Thus, functional language should be acceptable when the genus as claimed is sufficiently limited in scope (i.e., from *Bacillus* or *Bacillus stearothermophilus*) and the specification describes one or more species within that genus. Claim 1 recites the same type of functional claim language that was identified as acceptable in *Eli Lilly* given the

description of a single species by its nucleotide sequence. Thus, it should be evident that claim 1 (and claims dependent thereon) finds written descriptive support in the present application.

As demonstrated by Exhibits 1-3, one of ordinary skill in the art would have understood that applicants were in possession of the presently claimed invention at the time the present application was filed. This is so, because persons of skill in the art would have expected sufficiently related organisms from the genus *Bacillus* (and now *Geobacillus*) to possess homologous *holA* nucleotide sequences or delta subunit proteins. Exhibits 1-3 confirm this expectation to have been reasonable.

In view of all of the foregoing, applicants submit that the rejection of claims 1, 2, and 4-13 is improper and should be withdrawn.

The rejection of claims 1, 2, and 4-13 under 35 U.S.C. §112 (first paragraph) for lack of enablement is respectfully traversed.

It is the position of the PTO that the specification does not provide sufficient guidance for making and using other delta subunits within the scope of the claims. Applicants respectfully disagree.

The PTO is respectfully reminded that all that is needed is objective enablement of what is claimed. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The present application provides the nucleotide sequence of *Bacillus* (now *Geobacillus*) *stearothermophilus holA* (e.g., SEQ ID NO: 177) and describes how one of ordinary skill can isolate homologs of the disclosed sequence (see page 41, line 9 to page 42, line 29), express the delta subunit encoded by such homologous *holA* sequences (see Example 19, expressing *A. aeolicus* delta subunit), and test the encoded delta subunit for clamp loader assembly competence (see Examples 24 and 25, testing *A. aeolicus* clamp loader assembly) and for clamp loader activity (see Examples 26 and 30, testing *A. aeolicus* clamp loader activity). Thus, one of ordinary skill in the art would have been fully able to make and use DNA molecules and their encoded proteins within the scope of the presently claimed invention.

Moreover, with regard to method 3 for homolog identification, described at page 42, that is precisely the approach used to identify the *holA* homolog shown in Exhibit 1 (i.e., from other *Bacillus* or *Geobacillus* organisms). For this reason, it should be apparent that the present application fully enables the production and use of other species of *Bacillus* or *Bacillus* (now *Geobacillus*) *stearothermophilus holA* homologs.

In view of all of the foregoing, applicants submit that the rejection of claims 1, 2, and 4-13 for lack of enablement is improper and should be withdrawn.

Because 1 is allowable for the reasons noted above, applicants further submit that new claims 14-16 also are allowable. Because previous claim 3 was not rejected, applicants submit that new claims 17-21 are allowable.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 1, 2006

/Edwin V. Merkel/
Edwin V. Merkel
Registration No. 40,087

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603
Telephone: (585) 263-1128
Facsimile: (585) 263-1600

Exhibit 1



Search

Nucleotide

for

Go

Clear

Limits

Preview/Index

History

Clipboard

Details

Display

GenBank(Full)

Show 5

Send to

Range: from 2532557

to 2533603

Show whole sequence

 Reverse complemented strand Fe 1: BA000043. Reports *Geobacillus kaust...*[gi:56378377]

Links

Features Sequence

LOCUS BA000043 1047 bp DNA linear BCT 04-DEC-2004
DEFINITION *Geobacillus kaustophilus HTA426* DNA, complete genome.
ACCESSION BA000043 REGION: 2532557..2533603
VERSION BA000043.1 GI:56378377
KEYWORDS .
SOURCE *Geobacillus kaustophilus HTA426*
ORGANISM *Geobacillus kaustophilus HTA426*
Bacteria; Firmicutes; Bacillales; Bacillaceae; Geobacillus.
REFERENCE 1
AUTHORS Takami,H., Takaki,Y., Chee,G.J., Nishi,S., Shimamura,S., Suzuki,H., Matsui,S. and Uchiyama,I.
TITLE Thermoadaptation trait revealed by the genome sequence of thermophilic *Geobacillus kaustophilus*
JOURNAL (er) Nucleic Acids Res. 32 (21), 6292-6303 (2004)
PMID 15576355
REFERENCE 2 (bases 1 to 1047)
AUTHORS Takami,H., Takaki,Y. and Chee,G.
TITLE Direct Submission
JOURNAL Submitted (25-JUN-2003) Hideto Takami, Japan Marine Science and Technology Center, Microbial Genome Analysis Research Group; 2-15 Natsushima-cho, Yokosuka, Kanagawa 237-0061, Japan
(E-mail:takamih@jamstec.go.jp,
URL:<http://www.jamstec.go.jp/jamstec-e/bio/exbase.html>,
Tel:81-46-867-9643, Fax:81-46-867-9645)
FEATURES Location/Qualifiers
source 1..1047
/organism="Geobacillus kaustophilus HTA426"
/mol_type="genomic DNA"
/strain="HTA426"
/isolation_source="isolated from the deepest Ocean"
/db_xref="taxon:235909"
/note="thermophile"
gene complement(1..1047)
/locus_tag="GK2513"
CDS complement(1..1047)
/locus_tag="GK2513"
/codon_start=1
/transl_table=11
/product="hypothetical conserved protein"
/protein_id="BAD76798.1"
/db_xref="GI:56380890"
/translation="MLERVWGNIEKRQRSILLYLGYNEPFLITETYERLVNAALGPEE
REWNILAVYDCEETPVAALEEAETVPFFGERVILIKHPPFETSEKEKEIEHDLAKLE
AYLKAPSFFSIVVFFAPYEKLDERKKITKLAKEQSEVVIAAPLAEEAELRAWVRRRIES
QGAQASDEADVLIRRAGTQLSALANEIDKLALFAGSGGTIEAAAVERLVARTPEENV
FVIVEQVAKRDIFPALQTFYDLLENNEEPIKILALLAHAHFRLLSQVKWLASLGYGQAQ
IAAALKVHPFRVKLALAQAARFADGEGLAEAINELADADYEVKSGAVDRRLAVEILLMR

"WGTRPAQAGRHGRR"

ORIGIN

1 tcacccggc ccgtgacgccc cccgttgcac caggcggttg cccccaccgca tcaaaaaggcaq
61 ctcaacggcc aaccggcgat cgaccgcgttc gcttttcaact tgcgtatcggt cgtcagcgag
121 ctgttgtatc gcttcagcaa gcttcctcgcc agcgaagcggt gccgttgag caagagcgag
181 cttgacccgg aacgggttcca ctttgcggcgc cgcggcaatt tgcgttgcgc cgttagccaa
241 ggccggcaaggc catttcaactt gcggaaagcaa gcggaaatgg gcggcgagca gcggccaaat
301 tttgtatcggt ttttcatgtt tttcaaggcag atcataaaaac gtctgcacacg ccgttggaaat
361 gtcgcgttcc gccacttgtt cgcacaaaggcac aaatacgttt tcttccggcg tgcggggcgac
421 aaggccgttca accgcggcccg cctcgatggt tccgcggat ccggcaaaaca gggccaaattt
481 atcgatttca ttgcggcaagg cgggaaagctt cgtccccggcc cgccgcacca ggacatcaat
541 cgcctcgatcg ctgttgttgcg ccccttggctt ctcgtatcggt cgccgcaccc aggccgcgcag
601 ctccgcgttgcg gcgagcggtt cggcgatgtac gacttgcgtt tgctctttgg cgagcttcgt
661 aattttttttt cgcgtatcaa gcttctcgta cggcgccggaaa aaggacgacga tggaaaacgg
721 cgacccggcc ttcaagtacg cttccagctt cggccaaatca tggatgtatct ctttctcttt
781 ttcaagacgtg aaaaaatatg gatgtttgtat gaggatgaca cggccgtcgc cgaaaaacgg
841 caccgtctcg gcttccttcaa ggcggccctc gaccggcggtt tccgtcgagt cgtacacacgc
901 caaggttccac tccccgtctt cggggccaaag cgttgcgttc accaattcgct catacgtttc
961 cgttaataaaa aacggcttat tggcgatataa taataaaaga agagaaaaac gcccgttttc
1021 aatgtttccc catacggtttt ccagcat

//

[Disclaimer](#) | [Write to the Help Desk](#)
[NCBI](#) | [NLM](#) | [NIH](#)

Aug 15 2006 13:27:38

Exhibit 2

```

#####
# Program: needle
# Rundate: Wed Aug 23 05:36:23 2006
# Align_format: srspair
# Report_file: /ebi/extserv/old-work/needle-20060823-05382260401273.output
#####

#####
# Aligned_sequences: 2
# 1: SEQ_177
# 2: G_kaustophilus
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 1047
# Identity: 1030/1047 (98.4%)
# Similarity: 1030/1047 (98.4%)
# Gaps: 3/1047 ( 0.3%)
# Score: 6325.0
#
#
#####

SEQ_177      1 ATGCTGGAACCGGTATGGGAAACATTGAAAAACGGCGTTTTCGCCCT 500
G_kaustophilu 1 AtgctggAACCGGTATGGGAAACATTGAAAAACGGCGTTTTCGCCCT 500

SEQ_177      51 TTATTTATTATAACGCAATGAGCCGTTTTATTAAACGAAACGTATGAGC 1000
G_kaustophilu 51 ttatTTATTATAACGCAATGAGCCGTTTTATTAAACGAAACGTATGAGC 1000

SEQ_177      101 GATGGTGAACCGAGGCTTGCCCCGAGGAGCAGGGACTGGAACTGGCT 1500
G_kaustophilu 101 gatGGTGAACCGAGGCTTGCCCCGAGGAGCAGGGACTGGAACTGGCT 1500

SEQ_177      151 GTGTACGACTGGAGGAAACGCCATCGAGGCGGGCTTGAGGAGCCGA 2000
G_kaustophilu 151 gtgtacGACTGGAGGAAACGCCATCGAGGCGGGCTTGAGGAGCCGA 2000

SEQ_177      201 GACGGTCCGTTTCGGCGACGGCGTGTCAATTCTCATCAAGCATCCAT 2500
G_kaustophilu 201 gacGGTCCGTTTCGGCGAGCGGCGTGTCAATTCTCATCAAGCATCCAT 2500

SEQ_177      251 ATTTTTTACGTCTGAAAAAGAGAAGGAGATCGAACATGATTGGCGAAC 3000
G_kaustophilu 251 attttttACGTCTGAAAAAGAGAAGGAGATCGAACATGATTGGCGAAC 3000

SEQ_177      301 CTGGAGGCCTACTTGAAGGCGCCGTCGGCGTTTCGATCGTCGTCTTTTT 3500
G_kaustophilu 301 ctggaggcgtacttGAAGGCGCCGTCGGCGTTTCGATCGTCGTCTTTTT 3500

SEQ_177      351 CGCGCCGTACCGAGAACGCTGATCGAGGAAAAAAATTACGAAGCTGCCA 4000
G_kaustophilu 351 cgcGCCGTACCGAGAACGCTGATCGAGGAAAAAAATTACGAAGCTGCCA 4000

SEQ_177      401 AAGACCIAAGCGAAGTCGTCACTCGCGCCCGCTCGCGAACGCCAGCTG 4500
G_kaustophilu 401 aAGACCIAAGCGAAGTCGTCACTCGCGCCCGCTCGCGAACGCCAGCTG 4500

SEQ_177      451 CGTGCTGGGTGCGGCCCGCATCGAGAGCCAAGGGCGCAAGCAAGCGA 5000
G_kaustophilu 451 cgtGCTGGGTGCGGCCCGCATCGAGAGCCAAGGGCGCAAGCAAGCGA 5000

```

SEQ_177	501	CGAGGCCGATTGATGTCCCTGTTGGGGGGGGGGACGCAGCTTCCGCCT	550
G_kaustophilu	501	cgaggcgattgtatgtccctttggcgccggccggacgcagcttccgcct	550
SEQ_177	551	TGGCGAATGAAATCGATAAAATTGGCCCTGTTGCCGATCGGGCGGAACC	600
G_kaustophilu	551	tggcgatgaaatcgataaaattggccctgttgcggatcgccggacc	600
SEQ_177	601	ATCGAGGGCGGGCGGGTTGAGGGCTTCGCCCCACCCCGGAAGAAAA	650
G_kaustophilu	601	atcgaggcgccggcggttgaacggcttgtcgccgcacgcggaaagaaaa	650
SEQ_177	651	CGTATTTGTGCTTGCGACAAGTGCGCAAGCGCGACATTCCAGCAGCGT	700
G_kaustophilu	651	cgtatttgtcttgtcgagcaagtggcgaaagcgccgacattccagcggt	700
SEQ_177	701	TGCAGACGTTTATGATCTGCTTGAAAACAATGAAGGCCGATCAAATT	750
G_kaustophilu	701	tgcagacgtttatgatctgcttgaaaacaatgaagagccgatcaaatt	750
SEQ_177	751	TTGGCGTTCCTCGCCGCCATTCCGCTTGCTTTCGCAAGTGAANTGGCT	800
G_kaustophilu	751	ttggcgctgtcgccgcatttcgcgttgcgttgcgttgcgttgcgttgcgt	800
SEQ_177	801	TGCCTCTTCTAGGCTACGGACAGGCGCAAATTCTGCGGGCTCAAGCTGC	850
G_kaustophilu	801	tgcctcttaggctacggcgccgcaattgtcgccgcgtcaaggtgc	850
SEQ_177	851	ACCCGTTCCCGGTCAAGCTCGCTCTGCTCAAGCGGCCGCTTCGCTGAC	900
G_kaustophilu	851	accgttcccggtcaagctcgcttcgtcaagcgccgcgtcgac	900
SEQ_177	901	GGAGAGCTTCTGAGGCATCAACGAGCTCGCTGACCCCGATTACGAAGT	950
G_kaustophilu	901	ggagagcttgcgtggcgatcaacgagctcgctgcgttgcgttgcgttgcgt	950
SEQ_177	951	GAAAAGCGGGCGGTGATCGCCCGTTGGCGTTGAGCTGCTTCTGATGC	1000
G_kaustophilu	951	aaaaagcgccggcggtcgatcgccgttggccgttgcgttgcgttgcgt	1000
SEQ_177	1001	GCTGGGGCCACCCCGCCGCAAGCGGGGGGGCCACCCCGGGGG	1044
G_kaustophilu	1001	ggtggggcacccggccggcgcaugcgccggcggtcacggccggcggtga	1047

Exhibit 3

CLUSTAL W (1.83) Multiple Sequence Alignments

Sequence format is Pearson
Sequence 1: SEQ_178 348 aa
Sequence 2: G_kaustophilus 348 aa
Start of Pairwise alignments
Aligning...
Sequences (1:2) Aligned. Score: 99
Guide tree file created: [/ebi/extserv/clustalw-work/interactive/clustalw-20060823-05445443.dnd]
Start of Multiple Alignment
There are 1 groups
Aligning...
Group 1: Sequences: 2 Score: 7434
Alignment Score 2093
CLUSTAL-Alignment file created [/ebi/extserv/clustalw-work/interactive/clustalw-20060823-05445443.aln]

SEQ_178	MLERVGNIEKRRFSPLYLGYNEPFLLTETYRLVNAALGPEEREWNLAVIDCEETPIE	60
G_kaustophilus	MLERVGNIEKRRFSLILYLGNEPFLLTETYRLVNAALGPEEREWNLAVIDCEETPVE	60

SEQ_178	AALEEAETVPFFGERRVILIKHPYFFTSEKEKEIEHDLAKLEAYLKAPSFFSIVVFFAPY	120
G_kaustophilus	AALEEAETVPFFGERRVILIKHPYFFTSEKEKEIEHDLAKLEAYLKAPSFFSIVVFFAPY	120

SEQ_178	EKLDERKKITKLAKEQSEVVIAAPLAEELRAWVRRRIESQGAQASDEAIDVLLRAGTQ	180
G_kaustophilus	EKLDERKKITKLAKEQSEVVIAAPLAEELRAWVRRRIESQGAQASDEAIDVLLRAGTQ	180

SEQ_178	LSALANEIDKLALFAGSGGTIEAAAVERLVARTPEENVFLVEQVAKRDIPAAALQTFYDL	240
G_kaustophilus	LSALANEIDKLALFAGSGGTIEAAAVERLVARTPEENVFLVEQVAKRDIPAAALQTFYDL	240

SEQ_178	LENNEEPIKILALLAHAHFRLLSQVKWLASLGLYQQAQIAAALKVHPFRVKLALAQAARFAD	300
G_kaustophilus	LENNEEPIKILALLAHAHFRLLSQVKWLASLGLYQQAQIAAALKVHPFRVKLALAQAARFAD	300

SEQ_178	GELAEAINELADADYEVKSGAVDRRLAVELLLMRWGARPAAQAGRHR	348
G_kaustophilus	GELAEAINELADADYEVKSGAVDRRLAVELLLMRWGTRPAQAGRHR	348
